

SPL ER/DL SubTeam

Q&A Teleconference with FDA / DRLS Team

December 7, 2011

Questions/Responses

FDA participants:

- DRLS - Paul Loebach
- DRLS staff: Leyla Rahjou-Esfandiary, David Maczyk, Su Jin Park
- SPL Group - Lonnie Smith

1. When does a new NDC need to be created --ie when there is a change to the product's formulation/appearance or ownership (corporate merger):
Please lead a discussion on what kind of product changes would cause a change to the NDC code for the product. There have been recent validation errors and a refresher "course" might be useful.

Response:

- Refer to CFR 207.35 for details-- ie changes formulation, product name etc. In general, any change to formulation or appearance (physical characteristics) requires a new NDC.
- Imprint: while the regulations don't specifically state that this would require a new NDC, FDA is interpreting it that way. This is primarily a safety issue. If you update the information in the SPL, then the new SPL would supercede the old version. Thus, users would not be able to identify the old product that is still on the market.
- Corporate changes would not necessarily require a new NDC. If a company assumes another company's labeler code, and no imprint changes are implemented as a result, no NDC change needed
- Change in proprietary name would require a new name -- including optional "suffix" information in the proprietary name. Minor name changes (for example dropping the hydrochloride) may not require an NDC change.
- If you have questions, contact DRLS and they will evaluate it on a case-by-case basis.

2. New SPL requirement to add NDC codes to establishment information within the **drug listing** SPL:
We've heard of a future requirement to add NDCs to each establishment included in the SPL -- so that it is clear as to which establishments are in the supply chain for each product.
 - Will NDCs be required for just the establishments that are "manufacturers"? Or will NDCs be required for all establishments listed in the SPL, eg pack, labeler, analysis?
 - When will this new requirement be implemented?

Response:

- Currently in SPL, establishment information is in a separate section from the NDCs/packaging information. Thus FDA cannot match up an NDC to a specific establishment.
- A validation rule will be implemented that will require establishments to reference the product NDCs. Each product NDC must be linked to at least one establishment. This will allow a way to match -up the specific establishment to a specific product/NDC.
- Each product in the SPL must be linked to at least one establishment in the establishment section.

- When will this be implemented? In the meeting, the stated implementation timing was Jan 2, 2012. In post meeting conversations, the timing was changed to Feb 1, 2012.
- This validation rule has been published in the SPL implementation guide since 2010. It is currently in the new IG in section 4.1.5. SPL Vendors have had over a year to implement this change.
- Which business operations should be included? FDA instructs establishments to check all applicable specific business operations that apply so that it is clear in SPL what types of specific operations are being performed at that site.
- How can we encourage manufacturers to register the most specific business operations? The term "manufacture" is an overarching term that includes analysis, manufacture, pack, label, etc. DRLS is encouraging Pharma also needs to ask their contract partners to be specific.

Post meeting question:

What if we have multiple products (NDC Numbers all with the same first and second segments, but with different packaging configurations) that are manufactured at different plants?

- You only enter the NDC product code in the SPL -- first 2 segments of the NDC, not the entire 10 digit NDC code that includes the package code.
- FDA acknowledges that this doesn't get information specific down to the package size level. This was discussed at FDA, and they decided on using the product NDC code as a reasonable compromise -- to help limit the number of NDC numbers that sponsors would need to enter in the SPL.
- This coding is illustrated in the IG in section 4.1.5. The term "NDC product code" means the first 2 segments of the NDC number. The third segment is called the package code.
- Lonnie sent out an example of an SPL that includes this coding – see links below, refer to the establishment section, at the end of the SPL file:
 - As posted on DailyMed which has the product-to-establishment relationship:
<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?ndc=63459-548&start=1&labeltype=all>
 - As posted on FDA's access database:
<http://www.accessdata.fda.gov/spl/data/8ee1cd0e-bad7-48ff-9e25-8710edb812ec/8ee1cd0e-bad7-48ff-9e25-8710edb812ec.xml>
 - Note: as of Jan 4, 2012, Daily med has not updated their stylesheet to display these NDC codes. Use the link to the FDA access database.

3. Drug listing imported products by the manufacturer – ie using marketing category of "marketed exclusively for Private Label Distributors (PLD):"
 - Are manufacturers required to make drug listing submissions for products that they manufacturer exclusively for PLD. This was discussed earlier this year as a means to facilitate the importation process. Our imports are clearing customs even though we haven't submitted a separate drug listing. Please advise.
 - Related to question 2 above: Isn't this now redundant information since we will soon be required to include the NDC numbers for each product.
 - If we need to drug listing import from our foreign manufacturers, should the NDC number for the trade drug product appear in the XML? Or only the NDC number of the manufacturer?

Response:

- When there is a situation where a company makes a product for another company, and does not also package the product on its own, the company should list their product under one of the 'Manufactured for PLD' categories – to be in compliance.
- By selecting one of these categories, the contract manufacturer does not have to submit content of labeling. The SPL will not be displayed on DailyMed

- Mfgs must use their own labeler code in their drug listing, not the labeler code of the PLD.
- This does not preclude the PLD from listing. The PLD must also drug list under the appropriate categories – using its own labeler code. (Or the manufacturer may submit drug listing on behalf of the PLD – as a service to the PLD--using the labeler code of the PLD).
- Import agents may use their discretion at the point of entry – ie allowing material to be imported even if it hasn't been listed by the manufacturer --if they feel that all requirements have been met.
- DRLS still requires the drug listing (whether or not Imports acts)
- Some import agents may detain product at the port of entry. If there is an issue, the import officers can contact the DRLS office who can help determine if the product is drug listed.
- DRLS office cannot tell the import folks to release a shipment. DRLS can only confirm listing status.

Question from participant:

Is it appropriate for the PLD to ask their contract manufacturers to drug list?

- Yes! Pharma should contact the mfg and tell them that they are not in compliance with the regulations.

4. Drug Listing inner packs within a larger trade pack:
Pharma has recently received correspondence from the CMS group:

CMS has become aware of inner layer (pack) NDCs that are not electronically listed on the FDA New NDC Directory. If your organization has inner layer NDCs and would like these NDCs to be eligible for Medicare Part D coverage, please electronically list the NDCs separately to be included on the New NDC Directory. Please consider all NDCs with Labeler Codes with signed Medicare Coverage Gap Discount Program agreements.

We already are including these inner packaging in our current SPL. Why is CMS asking us to list them separately?

Response:

- SPL allows the display of all packaging layers. DRLS determined, in conjunction with discussions w/ CMS, that only the outermost package would be included in the NDC directory.
- Inner packs may be dispensed individually, and NDC codes are sometimes printed on inner packs for convenience to hospitals/pharmacies. Since these inner NDCs are no longer published in the NDC directory, this is causing confusion for CMS in reimbursement.
- If you need the inner package NDC to appear in the NDC directory, you should include the inner pack NDC as a separate package configuration in the SPL. Do not change the trade package, just add the inner pack as a stand-alone package.
- There is some internal discussion around this at FDA and they are seeking to resolve.

5. Duplicate SPL files on Daily Med – How to delete them:

Currently we have two SPL files on Daily Med with the same NDC Numbers. One SPL is an r3 file; the other is an r4 file. Pharma has been instructed to take one SPL file and enter Marketing End dates so this duplicate file would fall off of Daily Med. Is this the process DRLS recommends?

We are concerned that the same NDC Numbers appear on both SPL's so when I enter Marketing End dates in one file just to have one SPL removed from DM, will this cause the NDC Numbers to fall off the NDC Directory?

Response:

- DRLS doesn't want pharma to enter an "end marketing date" if the product is still on the market. This will cause confusion.
- Lonnie is working on a solution – it will involve making an update to the R3 file, because FDA does not want to be responsible for removing the wrong file. FDA is testing this now and will be publishing the process early next year.
- If you need to have this removed quickly, Lonnie can do this, but this is not the preferred process. Please wait until 2012 to use the new process/solution.

6. Daily Med – issue with deleting files – market end dates have been entered:
We have quite a few spl's where we have entered marketing end dates, and the files still remain on Daily Med.

- How long does it take to have these removed from Daily Med?
- Who should we contact to resolve the situation and get these removed?

Response:

- If you submit a file with a future end marketing date, the file will not be removed until the future date has been reached.
- If you submitted something with an end marketing date, then it should be removed promptly. You should confirm that it has been removed from the FDA repository.
- If the file isn't removed, then contact Daily Med to work through the removal.

7. NEW NDC Directory – Some NDC Numbers appear twice with two different "Start Marketing Dates". See example below. Why is this happening and how can Hospira clean up the Directory to reflect only one NDC Number with one Start Marketing Date?

- Example: 0409-1985

Response:

- DRLS changed their program for extracting data, which seems to have corrected some of the problem.
- DRLS confirmed that this NDC shows twice. They don't know the exact reason, but there is probably a second SPL (with a separate set ID) that is posted. The sponsor needs to remove/cancel out the erroneous SPL file
- Question: What happens if the look of the label changes- new logo, new colors, new look? Exact same product and NDC and text on the label. Do we enter a new market start date to reflect the new label?
 - Answer: No. Marketing start date is for when the product entered the market. If there is a label graphic type of change, that does not require a new market start date.
 - If you have already changed the market start date to reflect the new label, then just submit a new SPL with the corrected information.

8. Pre-launch importation of products:

Scenario: We have recently had shipments on hold with the following issue and would ask your guidance:

From FDA Compliance Officer: This entry is detained because of a misbranding issues. The NDC does not appear to be valid and does not cross-reference to a product. The NDC number for this product should be active prior to importation.

Response from Company: We have made 2 drug listings:

1. Manufacturers Drug Listing: (Company A in Italy is listed as manufacturer) NDC# 56789-111-xx (This drug listing was previously provided and submitted to FDA elist on 9/09/2011, marketing category is OTC Monograph drug product manufactured exclusively for private label distributor).

Product label with this shipment indicates NDC# 12345-111-xx as this will be the commercialized product label and there is not a bulk label indicating NDC# 56789-111-xx.

2. Commercialized finished product NDC# 12345-111-xx

Product is not in commercial distribution yet, and not scheduled to launch until 12/12/2011. This drug listing was provided and submitted to FDA eList on 10-20-11, initial marketing date is listed as 12/12/2011 so is not appearing on Daily Med or labels.fda.gov yet.

What can be done to confirm this product is not misbranded? From Compliance officer's feedback it appears the product should be active before importation, but this product is in launch build phase and will not be commercially released until scheduled launch date. Due to the confidential nature of this product, we did not want the label to appear on Daily Med prior to the launch date. Please also confirm which database FDA is looking up the information in and if they have their own database separate from Daily Med and labels.fda.gov.

Note: We were told by the SPL office that FDA Import staff should have access to this information as long as it has been elisted even though the product has not reached initial marketing date, but it appears this may not be the case. Please advise.

Response:

- What can be done at the point of entry? Import officers or the sponsor can contact DRLS about a listing issue. The import officer can confirm that the product is properly drug listed.
- Import staff does have access to these databases. All staff may not be completely trained. DRLS will help work things out as quickly as possible.
- DRLS cannot release a shipment – only Imports can do this.

9. Our SPL contains multiple NDC codes. However, not all of them are in the NDC directory.

Example

- There are several NDC Numbers on the SPLr4 file that have not posted on the NDC Directory (0409-7712-09, 0409-7713-09, 0409-7714-03, 0409-7715-02 and 0409-7715-03). NDC 0409-4031-01 does appear on the NDC Directory. Any idea why only 1 of the 6 NDC numbers appears on the NDC Directory?
- How we can get this cleaned-up?

Response:

- The new NDC directory should have fixed a lot of these issues.
- DRLS confirmed that all NDCs in the SPL are in the directory.

10. Business operations – Is there a way of obtaining information on business operations without contacting the company directly?

Response:

- This has come up before. Currently this information is not available. Paul Loebach forwarded this question to policy folks, and they are considering this request.

11. How can we correct information at drugs@FDA and within the Orange Book?

Example: Hospira received a letter from the FDA dated 08/26/97 confirming applications that were transferred from the Division of Metabolic and Endocrine Drug Products to the Office of Generic Drugs. The letter states, "This change in Center policy now permits the Office of Generic Drugs to assume the administrative and review functions of these applications as ANDAs pursuant to section 505(j) of the Act". The problem is Drugs@FDA and the Orange Book still show these as NDA's. Per Lonnie Smith this is causing an issue with some of our SPL files.

Can you offer advice on what we can we do to correct this?

Response:

- How did this happen? In the old days, FDA used to identify all NDAs and ANDAs numbers non-contiguously. Over the years, the databases have been updated and things got mixed up.
- DRLS does not impact or provide information to the Orange Book; Orange Book information comes directly from the Review Divisions.
- Go directly to review division and / or office of generic drugs and let them know there is an issue in the orange book. Ask for them to help resolve the issue.
- DRLS can provide the owner of the labeler code a list of all NDCs under a particular labeler code. [Send an e-mail request to DRLS and ask for a listings for firm report --the contact for that labeler needs to submit that e-mail.]